REMARKS

1. Preliminary Remarks

a. Status of Claims

Claims 21-51 are pending in this application. Claims 35-49 and 51 as well as SEQ ID NOS: 1-2078, 2080-3353 are withdrawn from further consideration to a nonelected invention because there are no allowable generic or linking claim. Applicant hereby notifies the Examiner of their intent to request rejoinder of Group II (claims 35-49 and 51) with Group I as well as SEQ ID NOS: 1-2078 and 2080-3353 upon allowance of linking claim 21 and claims 22-34 and 50.

Claims 21, 22, 24, 35, 36, and 38 are amended. Claim 49 is canceled. Claims 52-55 are new. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Upon entry of these amendments, claims 21-34, 50, and 52-55 are pending and under active consideration.

b. Amendment to the Claims

Claim 21 is amended in part wherein the first viral nucleic acid is 15-24 nucleotides, and wherein the two stem segments of the second viral nucleic acid each consists of 14-71 nucleotides and are at least 30.8% complementary. Support for claim 21 can be found Tables 2 and 3 of the specification. Claim 22 is amended to be directed to the nucleic acid of claim 21, wherein the first viral nucleic acid is at least 40.9% complementary to the mRNA. Support for claim 21 can be found in Table 4. Claim 24 is amended to be directed to the nucleic acid of claim 21, wherein the hairpin is characterized by a negative free energy of folding of at least –1.8 Kcal/mol. Support for claim 24 can be found at Table 2.

Withdrawn claim 35 is amended in part wherein the first viral nucleic acid is capable of forming a hairpin, wherein the two stem segments each consist of 14-71 nucleotides and are 30.8% complementary to each other. Support for claim 35 can be found in Tables 2 and 3 of the specification. Withdrawn clam 36 is amended to be directed to the nucleic acid of claim 35, wherein the second viral nucleic acid is at least 40.9% complementary to the mRNA. Support for claim 36 can be found in Table 4. Withdrawn claim 38 is amended to be directed to the nucleic acid of claim 35, wherein the hairpin is characterized by a negative free energy of folding of at least –1.8 Kcal/mol. Support for claim 38 can be found in Table 2.

New claim 52 is directed to the nucleic acid of claim 21, wherein the first viral nucleic acid consists of 18 to 24 nucleotides in length. New claim 53 is directed to the nucleic acid of claim 21, wherein the second viral nucleic acid consists of 50 to 120 nucleotides in length. New claim 54 is directed to the nucleic acid of claim 35, wherein the second nucleic acid consists of 18 to 24 nucleotides in length. New claim 55 is directed to the nucleic acid of claim 35, wherein the first viral nucleic acid consists of 50 to 120 nucleotides in length. Support for new claims 52-55 can be found throughout the

specification, for example, paragraph [0018] of the specification. Further discussion of the specification support that encompasses all the claims viral miRs and hairpins is provided below.

c. Request for Rejoinder

On page 2 of the Office Action, the Examiner did not find Applicant's traversal argument persuasive because independent claim 21 does not allegedly have a special technical feature over the prior art. As discussed below, the Examiner's cited art does not teach or suggest the claimed invention of claim 21 and therefore the instant application is unified. Nevertheless, as stated above, upon allowance of the generic claim 21, Applicant will request rejoinder of claims to Group II as well as SEQ ID NOS: 1-2078 and 2080-3353.

d. Information Disclosure Statement

On page 3 of the Office Action, the Examiner is considering the information disclosure statement of February 26, 2008 except citation No. C7, Barton et al, Evolution 2007, the Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY because the copy submitted for this citation does not correspond to the name of the citation nor is it legible. Applicant is in the process of acquiring a legible copy of the cited C7 reference and will submit via a Supplemental IDS.

2. Patentability Remarks

a. 35 U.S.C. §112, First Paragraph (Written Description)

On pages 4-7 of the Office Action, the Examiner rejects claims 21-34 and 50 under 35 U.S.C. §112, first paragraph, for allegedly lacking proper written descriptive support from the application as filed. Specifically, the Examiner asserts that Applicant has arbitrarily picked and choosen specific sequences to show support for claim limitations. The Examiner further alleges that the originally filed disclosure fails to provide the blaze marks to the specific claimed parameters (*citing Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320 (Fed. Cir. 2000). Applicant traverses the rejection.

As stated before, the Examiner must take into account which numerical range limitations one of skill in the art would consider inherently supported by discussion in the original disclosure (see M.P.E.P. §2163.05 III). Nevertheless, in order to expedite prosecution, Applicant has amended the claims to recite either the appropriate range in various nucleotide lengths or minimal requirement of percent complementation or hairpin free energy to encompass the claimed structural features of each and every viral miRNA and hairpin precursor discussed in the application.

All of the disclosed and amended claimed viral hairpin precursors and viral mature miRNAs possess the following common attributes and features as indicated in the Table below.

Viral Structure	Viral Feature	Support
Viral Hairpin	50 to 131 nucleotides in length	Table 2, Example: Table 2, lines 2891-2895 showing viral hairpin SEQ ID NO: 1020 at a length of 50 nucleotides and Table 2, lines 253-261 viral hairpin SEQ ID NO: 644 at a length of 131 nucleotides, wherein Table 2 provides all other nucleotide lengths between 50 to 131.
Viral Hairpin	Two Stem Segments that each are 14 to 71 nucleotides in length.	Page 4, line 29; and Table 2 in general; Example Table 2, lines 1245-1248 showing a length of 15 nucleotides for a stem segment of viral hairpin SEQ ID NO: 883 and Table 2, lines 8569-8577 showing a length of 71 nucleotides for a stem segment of viral hairpin SEQ ID NO: 251, wherein Table 2 provides all other examples of two stem segments between 14 to 71 nucleotides in length..
Viral Hairpin	Intervening Loop 3 to 19 nucleotides	Table 2 in general; Example Table 2, lines 37-31 showing a hairpin loop of 3 for viral hairpin SEQ ID NO: 625 and Table 2, lines 7505-7512 showing a hairpin loop of 19 for viral hairpin SEQ ID NO: 1302, wherein Table 2 provides all other examples of intervening loops between 3 to 19 nucleotides.
Viral Hairpin	At least 30.8% complementation between first and second segments of hairpin	Table 2, ; Example, Table 2 lines 4402-4406 showing 30.8% complementarity percentage between first and second segments of hairpin
Viral Hairpin	-1.8 Kcal/mol	Table 2; Example Table 2 lines 1178-1181 showing a –1.8 Kcal hairpin free energy
Viral miRNA	15 to 24 nucleotides in length	Table 3, Example Table 3, line 3568 showing viral miR SEQ ID NO: 2966 at a length of 15 nucleotides; and Table 3 providing all other miRNA lengths between 15 to 24 nucleotides in length
Viral miRNA	Binds trans related mRNAs	Page 4, line 29
Viral miRNA	Capable of inhibiting protein expression	Page 6, line 1
Viral miRNA	At least 40.9% complementation between miRNA and target mRNA	Table 4; Example Table 4, lines 1401338-1401344 for viral miR SEQ ID NO: 1699 binding target gene sequence UBE21G1.

These common claimed attributes or features are at the minimum and maximum numerical ranges for either length limitations, percent complementation, or negative folding energy of the claimed viral hairpin and miRs. Specifically, all of the claimed viral hairpins are between 50 and 131 nucleotides in length, contain two stem segments that are between 14 to 71 nucleotides in length, have intervening loops between 3 to 19 nucleotides in length, possess at least 30.8% complementation between the first and second segments of the hairpins, and have a negative hairpin folding energy at least –1.8 Kcal/mol. All of the claimed viral miRs are between 15 to 24 nucleotides in length, possess at least 40.9% complementation between the miRNA sequence and target mRNA sequence, bind trans related mRNAs and are capable of inhibiting protein expression. In view of the foregoing amendment and remarks, Applicant submits that the rejection of claims 21-34 and 50 under 35 U.S.C. §112, first paragraph, for

allegedly failing to comply with the written description requirement has been overcome and should be withdrawn.

b. 35 U.S.C. §102(e)

Zamore (U.S Pat. Appl. Pub. No. 2006/0009402)

On pages 7 and 8 of the Office Action, the Examiner rejects claims 21, 22, 25, 33, and 34 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Appl. Pub. No. 2006/0009402 (Zamore). Specifically, the Examiner asserts that Zamore teaches isolated miRNA precursors comprising sequence of the mature miRNA and a hairpin sequence and the mature miRNA binds and inhibits mRNA transcription from a viral genome. Applicant respectfully disagrees.

Zamore does not recite a viral hairpin precursor or miRNA sequence in anyway. Rather, Zamore teaches a non-natural synthetic sequence that when processed in the cell produce small interfering RNAs (siRNAs) (*e.g.*, paragraph 0006, 0049, sequence listing). The Examiner has failed to point or show a single "viral" sequence let alone one possessing all of the other structure features required in claims 21, 22, 25, 33, and 34. The fact that the Zamore sequence, which is not a viral sequence, produces siRNAs that regulate viral sequences is irrelevant because the claims do not require that the target genes be viral, but rather that the miRNA sequence be viral. In view of the foregoing, Applicant respectfully submits that the rejection of claims 21, 22, 25, 33, and 34 under 35 U.S.C. §102(e) as being anticipated by Zamore has been overcome and should be withdrawn.

Cullen (U.S. Pat. Appl. Pub. No 2004/0053411)

On page 8 of the Office Action, the Examiner rejects claims 21, 22, 25, 33, and 34 under 35 U.S.C. §102(e) as being anticipated by U.S. Pat. Appl. Pub. No. 2004/0053411(Cullen). Specifically, the Examiner asserts that Cullen teaches isolated nucleic acids that encode miRNA precursors that comprise mature miRNAs, which induce degradation of the mRNA transcript of a target gene sequence or inhibit translation of the mRNA. Applicant respectfully disagrees.

Like Zamore, Cullen fails to teach or suggest a viral hairpin precursor or miRNA sequence in anyway. Rather, Cullen teaches non-natural (*i.e.*,"artificial') sequences based upon using the prescursor sequence of miR-30, a human hairpin sequence isolated from HeLa cells lines as discussed in paragraph 0044 and 0053 of Cullen. Cullen used the human precursor sequence of miR-30 to generate artificial miRNA precursor sequences that would generate miRNA in human cells. Cullen substitutes stem sequences of the human miR-30 precursor sequence in constructing artificial precursor miRNA sequences that generate an miRNA that target mRNA such as Drosophila nxt gene (see paragraphs 0051, 0052).

Again, the Examiner has failed to point or show a single sequence of Cullen that is viral or will produce a viral sequence let alone possess all of the other structure features required in claims 21, 22, 25, 33, and 34. The fact that an "artificial miRNA precursor" of Cullen, which is not a viral sequence, but

based upon the human miR sequence, may produces siRNAs that regulate viral sequences is irrelevant (see paragraph 0027 of Cullen) because the claims do not require that the target genes be viral, but rather that the miRNA and hairpin precursor sequence be viral. In view of the foregoing, Applicant respectfully submits that the rejection of claims 21, 22, 25, 33, and 34 under 35 U.S.C. §102(e) as being anticipated by Cullen has been overcome and should be withdrawn.

Khvorova et al., US 2007/0031844

On page 9 of the Office Action, the Examiner rejects claims 21, 22, 33, 34, and 50 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Appl. Pub. No. US2007/0031844 (Khvorova). Specifically, the Examiner asserts that Khvorova teaches a nucleic acid that is 19 nucleotides in length and at least 72.7% identical to the nucleotide sequence of SEQ ID NO: 2079. Applicant respectfully submits that the Examiner has misconstrued the scope of the claim 21 and claim 22.

Specifically, claims 21 and 22 are not directed to variants of the claimed viral miRNA nucleic acids. Rather, claim 22 is directed to the nucleic acid of claim 21 wherein the first nucleic acid (miRNA viral sequence) is at least 40.9% complementary to a target mRNA sequence. This claim language has nothing to do with encompassing variants of a miRNA sequence such as SEQ ID NO: 2079. In terms of SEQ ID NO: 2079, claim 22 simply requires that the viral miRNA sequence of SEQ ID NO: 2079 be at least 40.9% complementary to a target mRNA sequence. Even if SEQ ID NO: 1360090 of Khvorova happens to be 72.7% identical to SEQ ID NO:2079, the Khvorova sequence does not possess the structural or functional requirements of claim 21, let alone the sequence requirements of claim 50 as it relates to SEQ ID NO: 2079. Accordingly, the failure of SEQ ID NO: 1360090 to anticipate claim 21 in turn fails to anticipate dependent claims 22, 33 (probe), 34 (vector), and 50 as well. In view of the foregoing, Applicant submits that the rejection of claims 21, 22, 33, 34, and 50 under 35 U.S.C. §102(e) over Khvorova has been overcome and should be withdrawn.

Buxton et al., WO2004/053157

On page 9 and 10 of the Office Action, the Examiner rejects claims 21, 22, 33, and 50 under 35 U.S.C. §102(e) as being anticipated by WO2005/053157 (Buxton). Specifically, the Examiner asserts that Buxton teaches a nucleic acid of SEQ ID NO: 89 that is 18 nucleotides in length and at least 72.7% identical to SEQ ID NO: 2079. Similar to the analysis of Khvorova, Applicant respectfully submits that the Examiner has misconstrued the scope of claims 21, 22, and 50.

Specifically, claim 22 is directed to the nucleic acid of claim 21 wherein the first nucleic acid (miRNA viral sequence) is at least 40.9% complementary to a target mRNA sequence. This claim language has nothing to do with encompassing variants of a miRNA sequence such as SEQ ID NO: 2079. In terms of SEQ ID NO: 2079, claim 22 simply requires that the viral miRNA sequence of SEQ ID NO:

2079 be at least 40.9% complementary to a target mRNA sequence. Even if SEQ ID NO: 89 of Buxton is at least 72.7% identical to SEQ ID NO:2079, the Buxton sequence does not possess the structural or functional requirements of claim 21, let alone the sequence requirements of claim 50 as it relates to SEQ ID NO: 2079. In view of the foregoing, Applicant submits that the rejection of claims 21, 22, 33, and 50 under 35 U.S.C. §102(e) over Buxton has been overcome and should be withdrawn.

Stacey et al., WO00/31540

On page 10 of the Office Action, the Examiner rejects claims 21, 22, 33, and 50 under 35 U.S.C. §102(e) as being anticipated by WO00/31540 (Stacey). Specifically, the Examiner asserts that Stacey teaches a nucleic acid of SEQ ID NO: 10 that is 20 nucleotides in length and at least 72.5% identical to SEQ ID NO: 2079. Similar to the analysis of Khovora and Buxton, Applicant respectfully submitst that the Examiner has misconstrued the scope of claims 21, 22, and 50.

Again, claim 22 has nothing to do with encompassing variant of the miRNAs of claim 21 let alone the miR sequence of SEQ ID NO: 2079. Claim 22 simply requires that the viral miRNA sequence of claim 21 be at least 40.9% complementary to a target mRNA sequence. Even if SEQ ID NO: 10 of Stacey is at least 72.7% identical to SEQ ID NO: 2079, the Stacy sequence does not possess the structural or functional requirements of claim 21, let alone the requirements of claim 50 as it relates to SEQ ID NO: 2079. In view of the foregoing, Applicant submits that the rejection of claims 21, 22, 33, and 50 under 35 U.S.C. §102(e) over Stacey has been overcome and should be withdrawn.

c. 35 U.S.C. §103(a)

On pages 11-13 of the Office Action, the Examiner rejects claims 21-34 and 50 under 35 U.S.C. §103(a) as being unpatentable over Ambros (Cell 107:823-826 (2001))(Ambros) in view of Lai et al (Genome Biology 4:R42 (2003))(Lai) and Knipe et al., PNAS 76:4534-4538 (1979)) (Knipe).

Applicant submits that the new rejection has the same deficiencies as previously addressed in the Office Action dated September 26, 2007. Specifically, the Examiner has failed to address the previously submitted evidence regarding the uncertainty of identifying viral miRNAs and miRNA precursors, as discussed in Applicant's previous response of February 26, 2008, which are incorporated by reference. As Applicant has previously argued, at the time of filing of the instant application, miRNAs were believed to exist only in a few eukaryotic branches of the phylogenic tree (i.e., vertebrate animals, invertebrate animals, and plants). The Examiner has presented no evidence whatsoever to suggest that one of ordinary skill would have expected miRNAs to be present in the more divergent branches of the phylogenic tree such as bacteria or viruses. Moreover, the Examiner has failed to address the practical considerations that led to a doubt that miRNAs existed in viral genomes due to their small size and lack of intergenic space compared to the genome size and intergenic space of Drosophila or organisms.

Applicant submits that the new rejection centered on Lai does nothing to address the evidence of uncertainty submitted by the Applicant. Instead, Lai has the same inherent flaws as the previous relied on references of Moss *et al., Current Biology* 12:R138-R140 (2002) (hereafter "Moss"), and Grad *et al., Molecular Cell* 11:1253-1263 (2003) (hereafter "Grad"). Specifically, miRseeker of Lai relies on miRNA sequences conserved across **bilaterian evolutionary related species** (i.e., complex eukaryotes) to identify new miRNA sequences and precursors. *See* page 2, first column lines 7-12; second column, lines 1 and 2 of second full paragraph; page 4, second column, first full paragraph.

As concluded by Lai, "the approach used in this study should be applicable to the analysis of other sets of sequenced genomes of related **higher eukaryotic model organisms**." *See* page 17, first column, second full paragraph 11-13. Clearly, Lai is limited to the identification of miRNAs within a few small branches of the phylogenic tree—a limited number of complex eukaryotes such as vertebrate animals (humans, mice, and rats), invertebrate animals (C. elegans, Drosophila), and plants. While the cited references disclose that computational methods may be useful to identify new miRNAs in the genomes of highly related eurkaryotes such as worms, flies, humans, and perhaps all animals, the cited references fails to state or demonstrate in any way miRNAs were expected to be present divergent single cell organisms (such as bacteria or yeast) or acellular organisms such as fungi, let alone viruses.

Neither Ambros nor Knipe remedy the deficiencies of Lai. Ambros focuses on identifying miRNAs only in the same complex eukaryotic species discussed and referenced in Lai (i.e., vertebrates, invertebrates, and plants), and provides no evidence that miRNAs were expected to be present in divergent single cell organisms, acellular organism, or viruses. Knipe simply provides the HSV-1 genome and does nothing to overcome the failings of Ambros in view of Lai. Accordingly, Applicant submits that the Examiner has failed to provide a prima facie case of obviousness of claims 21-34 and 50 over Ambros in view of Lai and Knipe. Therefore, the Applicant respectfully requests that the rejection of claims 21-34 and 50 under 35 U.S.C. §103(a) has been overcome and should be withdrawn.

d. Nonstatutory Obviousness-Type Double Patenting

On pages 13-16 of the Office Action, the Examiner rejects claims 21, 22, and 25-34 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-8 and 12 of copending U.S. Patent Appl. No. 10/605,838. The Examiner also provisionally rejects claims 21-23, 25, 27, 28, 33, and 34 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-6 of U.S. Patent Appl. No. 10/604,942. The Examiner further provisionally rejects claims 21-23, 25, 27, 28, 33, and 34 on the group of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 34-37 of copending U.S. Patent Appl. No. 10/707,003. The Examiner rejects claims 21-23, 25, 27, 28, 33, and 34 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 23, 36, and 39 of

copending U.S. Patent Appl. No. 10/604,943. The Examiner separately rejects claims 21-23, 25, and 30-34 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 22, 34, and 46 of copending U.S. Patent Appl No. 10/604,943.

Applicant respectfully requests that the Examiner hold the rejection in abeyance until there is allowable subject matter, at which time the Applicant will consider amending the claims in U.S. Patent Appl. Nos. 10/605,838, 10/604,942, 10/604,943, or 10/707,003, or filing a terminal disclaimer.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: March 16, 2009

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